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CLINICAL INVESTIGATION **Lung**

SELECTIVE NODAL IRRADIATION ON BASIS OF ^{18}FDG-PET SCANS IN LIMITED-DISEASE SMALL-CELL LUNG CANCER: A PROSPECTIVE STUDY

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Purpose: To evaluate the results of selective nodal irradiation on basis of ^{18}F-deoxyglucose positron emission tomography (PET) scans in patients with limited-disease small-cell lung cancer (LD-SCLC) on isolated nodal failure.
Methods and Materials: A prospective study was performed of 60 patients with LD-SCLC. Radiotherapy was given to a dose of 45 Gy in twice-daily fractions of 1.5 Gy, concurrent with carboplatin and etoposide chemotherapy. Only the primary tumor and the mediastinal lymph nodes involved on the pretreatment PET scan were irradiated. A chest computed tomography (CT) scan was performed 3 months after radiotherapy completion and every 6 months thereafter.
Results: A difference was seen in the involved nodal stations between the pretreatment ^{18}F-deoxyglucose PET scans and computed tomography scans in 30% of patients (95% confidence interval, 20–43%). Of the 60 patients, 39 (65%; 95% confidence interval [CI], 52–76%) developed a recurrence; 2 patients (3%, 95% CI, 1–11%) experienced isolated regional failure. The median actuarial overall survival was 19 months (95% CI, 17–21). The median actuarial progression-free survival was 14 months (95% CI, 12–16). 12% (95% CI, 6–22%) of patients experienced acute Grade 3 (Common Terminology Criteria for Adverse Events, version 3.0) esophagitis.
Conclusion: PET-based selective nodal irradiation for LD-SCLC resulted in a low rate of isolated nodal failures (3%), with a low percentage of acute esophagitis. These findings are in contrast to those from our prospective study of CT-based selective nodal irradiation, which resulted in an unexpectedly high percentage of isolated nodal failures (11%). Because of the low rate of isolated nodal failures and toxicity, we believe that our data support the use of PET-based SNI for LD-SCLC. © 2010 Elsevier Inc.

Selective nodal irradiation, small cell lung cancer, positron emission tomography, PET, combined modality treatment, elective nodal irradiation.

INTRODUCTION

The prognosis of patients with limited-disease small-cell lung cancer (LD-SCLC) has improved significantly with the application of accelerated radiotherapy (RT) and concurrent chemotherapy (1), which have become the current standard treatment. Although long-term survival rates of approximately 25% have been reached, more than 30% of patients will still develop local failure with this treatment (1). Improving locoregional tumor control by simply increasing the radiation dose is not straightforward, because dose-limiting toxicity occurs, consisting of severe reversible esophagitis and lung damage (2–4). An attractive strategy to reduce the toxicity is to diminish the radiation fields by omitting routine elective nodal irradiation (ENI) of the mediastinum. This strategy has proved its efficacy in non–small-cell lung cancer (NSCLC), in which radiation fields could be safely reduced by selective nodal irradiation (SNI), using computed tomography (CT), and even further using ^{18}F-deoxyglucose (FDG)

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positron emission tomography (PET) scans (5–8). Treating only FDG-positive mediastinal areas decreased the radiation exposure to the lungs and the esophagus sufficiently to allow for dose escalation in NSCLC (9, 10). Although selective irradiation of clinically involved nodes is also regularly applied in clinical practice for SCLC, no published data are available supporting this practice. A recent report from the International Atomic Energy Agency meeting emphasized the need for prospective clinical evidence regarding SNI for SCLC (11).

To date, only a few prospective data concerning SNI for SCLC are available. In a previous Phase II trial from our group, isolated nodal failures were observed outside of the clinical target volume (CTV) in 11% of patients undergoing SNI, using CT (12). These isolated nodal failures all occurred in the ipsilateral supraclavicular fossa. Baas *et al*. (10) and Belderbos *et al*. (13) reported an isolated nodal recurrence in the ipsilateral supraclavicular fossa in 1 of 36 patients treated with concurrent chemotherapy and CT-based involved field irradiation. Although no definitive conclusions could be drawn because of the small sample size, those findings imply that the safety of SNI in NSCLC cannot be straightforwardly extrapolated to SCLC patients. The available data suggest that FDG-PET scans are more accurate than CT in the primary staging of SCLC (14–17). In a planning study on FDG-PET–based selective mediastinal node irradiation in 21 LD-SCLC patients to investigate the potential role of FDG-PET in RT planning (18), we found a change in the treatment plan compared with the CT-based plan in 24% of patients. Because of these results, we decided to prospectively evaluate SNI based on FDG-PET for LD-SCLC. Our primary endpoint was to evaluate the proportion of isolated nodal failures; the secondary end points were the patterns of recurrence and esophageal and pulmonary toxicity.

METHODS AND MATERIALS

Patient population

Patients diagnosed with LD-SCLC and referred for radical RT to Maastro Clinic between December 2004 and November 2006 were prospectively evaluated. The inclusion criteria were cytologically or histologically proven SCLC; limited disease, defined as International Union Against Cancer Stage I-III, with the exclusion of T4 lesions because of malignant pleural or pericardial effusion; World Health Organization performance status 0–2; age ≥18 years; and adequate pulmonary function (forced expiratory volume in 1 second >1 L). Patients with severe recent cardiac disease (*e.g.,* arrhythmia, congestive heart failure, infarction) were excluded. The minimal follow-up time after the start of RT was 18 months.

Staging

All patients underwent bronchoscopy with biopsy and standard hematologic and biochemical workup. Brain imaging was performed with either magnetic resonance imaging or a contrast-enhanced CT. Pretreatment imaging of the chest consisted of either a whole body FDG-PET scan and a contrast-enhanced CT scan of the chest or a combined whole body FDG-PET and CT scan with contrast.

Chest imaging with FDG-PET and CT

For PET-based RT planning, a combined PET-CT scan was performed either during the diagnostic process only or during both the diagnostic process and for RT simulation. In both cases, to ensure optimal co-registration, the PET-CT scan was obtained with the patient in the RT position with both arms above the head (19). Patients had to have fasted for ≥6 h before the examination. The injected total activity of FDG was calculated from the weight of the patient: weight × 4 + 20 MBq. After a rest period of 60 min (interval needed for FDG uptake), the PET and CT images were acquired. A CT scan of the whole thorax was performed with intravenous contrast during free breathing.

Lymph nodes were judged positive and included in the CTV on basis of the report of the PET and CT scans. The CT and PET findings were interpreted and reported independently by an experienced chest radiologist and nuclear medicine specialist, respectively.

The CT findings from the diagnostic CT scan were also interpreted by an experienced chest radiologist. Lymph nodes were considered to be pathologic on CT when their axial diameter was >1 cm. The lymph nodes were considered positive on the FDG-PET scan on basis of visual interpretation by an experienced PET scan specialist. No quantitative standardized uptake value threshold was used, because a visual scale has been shown to be at least as accurate as the use of a standardized uptake value threshold to distinguish benign from malignant nodes (20, 21). The involved lymph node stations were recorded according to the Mountain and Dresler classification scheme (22).

Radiotherapy

For RT planning, contrast-enhanced CT or combined FDG-PET-CT was performed that extended from the cricoid to the second lumbar vertebra, with a maximal slice thickness of 3 mm. Patients were scanned in the supine position with both arms above the head. The CT and PET images were automatically registered using a rigid registration technique based on mutual information and were subsequently fused using Focal software (Computerized Medical System [CMS], St. Louis, MS). RT planning was performed with a XiO treatment planning system (CMS), using inhomogeneity corrections based on a convolution algorithm. For all patients, the gross tumor volume (GTV) and planning target volume (PTV) were defined on basis of the PET and CT data. In the case of induction chemotherapy, the postchemotherapy volume was considered the GTV of the primary tumor, whereas for the lymph nodes, only the pretreatment extension was considered. For the primary tumor, the GTV was delineated using the CT findings only, using lung window settings (W = 1,700, L = −300). We deliberately avoided contouring on the basis of ill-defined areas on the PET scan. Instead, the sharp boundaries of the CT scan images were used. For planning of the lymph nodes, the pretreatment anatomic sites of the involved zones on the FDG-PET scan were delineated on the planning CT scan in a mediastinal window setting (W = 600, L = 40). The whole pathologic anatomic region as described by the nuclear medicine specialist in the original diagnostic report (*i.e.,* before the start of chemotherapy) was delineated (23). If the PET scan was negative in the mediastinum and the CT scan positive, the mediastinum was not included in the GTV. The margin from the GTV to the CTV was 5 mm, and from the CTV to the PTV was 5 mm for the nodal areas and 10 mm for the primary lung tumor. No elective nodal irradiation was performed.

Contouring of the lung was done automatically by the treatment planning system. The mean lung dose (MLD) was analyzed as a possible predictor for radiation pneumonitis. For the calculation of the

Table 1. Toxicity grading criteria according to Common Terminology Criteria for Adverse Events, version 3.0

Adverse event	Grade				
	1	2	3	4	5
Esophagitis	Asymptomatic; pathologic, radiologic or endoscopic findings only	Symptomatic; altered eating/swallowing (*e.g.,* altered dietary habits, oral supplements); intravenous fluids indicated <24 h	Symptomatic and severely altered eating/ swallowing (*e.g.,* inadequate oral caloric or fluid intake); intravenous fluids, tube feedings, or total parenteral nutrition indicated ≥24 h	Life-threatening consequences	Death
Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic, narcotic medication indicated	Symptomatic, significantly interfering with sleep or activities of daily living	—	—
Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion, unable to walk 1 flight of stairs or 1 city block (0.1 km) without stopping	Dyspnea with activities of daily living	Dyspnea at rest; intubation or ventilator indicated	Death

MLD, the volume of both lungs minus the GTV was considered (24). The dose constraint to the lungs was set at a MLD of 19 Gy. The esophagus was delineated from just below the larynx to the gastroesophageal junction. Neither the GTV nor the PTV was subtracted from this volume. The mean esophageal dose (MED) and the maximal esophageal dose (Dmax) were analyzed as possible predictors of early and late esophageal toxicity (24, 25). The spinal cord was drawn throughout the whole CT scan and was considered to be at the inner margin of the bony spinal canal. The maximal allowed dose to the spinal cord was 54 Gy, and this dose constraint was not reached in the present study.

All patients were treated with a three-dimensional conformal treatment plan using 6–10-MV photons. The prescribed dose to the PTV was 45 Gy in 30 fractions within 3 weeks (1.5 Gy twice daily, with a minimal interval between two fractions of 8 h) according to the International Commission on Radiation Units and Measurements report 50 guidelines (26). During RT, patients were seen weekly by the radiation oncologist for the evaluation of acute side effects.

Chest RT was planned to start as early as possible after the beginning of chemotherapy. After thoracic irradiation and 5 cycles of chemotherapy, repeat staging was performed, including a chest X-ray and contrast-enhanced CT scan or magnetic resonance imaging of the brain. If no progression was found on the chest X-ray and no brain metastases were seen, the patients were offered prophylactic cranial irradiation (PCI) to a dose of 25 Gy in 10 fractions.

Chemotherapy

Patients underwent chemotherapy according to the standard protocol in the Comprehensive Cancer Centre Limburg (The Netherlands). The standard protocol was carboplatin on Day 1 and etoposide (120 mg/m^2) on Days 1–3. The carboplatin dose was based on the target area under the curve (5 mg/mL/h) × (glomerular filtration rate + 25), with the glomerular filtration rate calculated according to the Cockroft-Gault formula. The chemotherapy cycles were repeated every 21 days for a total of 5 cycles.

Post-treatment follow-up

The follow-up consisted of a visit 3 weeks after the end of RT for the evaluation of acute side effects. Thereafter, visits every 3 months, including history taking and physical examination, were performed, for the first 2 years. After this period, 6-month visits were performed until 5 years after treatment. CT of the thorax was performed 3 months after RT completion and every 6 months thereafter. When a patient presented with a recurrence outside of the follow-up visits, chest imaging was performed with chest X-ray and CT. After the detection of a recurrence, the follow-up visits were continued at 3-month intervals, with the type of imaging guided by the site of progression and the presence of symptoms.

Local tumor control was evaluated according to the criteria of Green *et al*. (27). An isolated nodal recurrence was defined as recurrence in the regional nodes outside the CTV, in the absence of in-field failure or distant metastases.

The pulmonary and esophageal toxicity were scored according to the Common Terminology Criteria for Adverse Events, version 3.0 (Table 1) (28). Toxicity was scored before the start of RT, at the weekly visits during RT, and at the follow-up visits.

Ethics

The trial was performed in accordance with the Dutch laws and regulations. The study protocol was registered at the National Institutes of Health clinical trial database, under NCT00572923.

Statistical analysis

On basis of the planning study we had previously performed (18), we hypothesized that introducing PET into the RT planning would change the treatment fields in 25% of the patients compared with CT-based planning (29). From the results of PET-based SNI for NSCLC, we expected the percentage of isolated nodal failures to not exceed 5%. As the upper bound of the 95% confidence interval (CI), we used the observed 11% of isolated nodal failures with CT-based SNI (12). To detect this rate of failures, ≥50 patients were needed for the present study (30).

Table 2. Baseline patient and treatment characteristics

Characteristic	Value (+/−SD)
Age (y)	
Median	66.0 ± 8.9
Range	48–55
Gender	
Male	40 (66.7)
Female	20 (33.3)
WHO performance status	
0	13 (21.7)
1	39 (65.0)
2	8 (13.3)
Lung function (median FEV_1; %)	70.0 ± 20.2
Tumor location	
Right upper lobe	17 (28.3)
Right middle lobe	5 (8.3)
Right lower lobe	4 (6.7)
Left upper lobe	1 (18.3)
Left lower lobe	6 (10.0)
Right hilus	7 (11.7)
Left hilus	8 (13.3)
Unknown	2 (3.3)
Chemotherapy	
Carboplatin-etoposide	58 (96.7)
Carboplatin-paclitaxel	1 (1.7)
Unknown	1 (1.7)
Interval between CTx and RT (d)	
Mean	27.8
Range	13–158
Dose (Gy)	
45	59 (98.0)
54	1 (2.0)
OTT of RT	
Median	21.0 ± 3.7
Range	17–41
SER	
Median	39.0
Range	20–176

Abbreviations: WHO = World Health Organization; FEV_1 = forced expiratory volume in 1 s; CTx = chemotherapy; RT = radiotherapy; OTT = overall treatment time; SER = interval between start of CTx and end of RT.

The results are expressed as the mean ± standard deviation (SD) or as a proportion, with the 95% CIs. The estimates of overall survival (OS) and progression-free survival rates were calculated with the Kaplan-Meier method, on an intent-to-treat basis, starting from the first day of RT. Correlations between the dose–volume parameters and toxicity were calculated using a two-sided Spearman's test or a chi-square test in the case of nominal variables.

RESULTS

Patient and treatment characteristics

A total of 60 patients with LD-SCLC, referred to our institution between December 2004 and November 2006, were included. The baseline patient characteristics are summarized in Table 2. Most patients were male (67%). All patients received chemotherapy, which in 97% consisted of carboplatin-etoposide. One patient received carboplatin-paclitaxel, because she was diagnosed with ovarian cancer during the diagnostic workup. A total of 59 patients (98%) received a dose of 45 Gy. Five patients were treated with sequential chemoradiotherapy instead of concurrent chemoradiotherapy. The reasons for this protocol violation were either a too high MLD owing to the size of the primary tumor or a delay in patient referral. One patient was not considered fit enough to undergo accelerated RT with concomitant chemotherapy and was therefore treated with 5 cycles of induction chemotherapy, followed by RT to a dose of 54 Gy in 30 once-daily fractions.

The median interval between the first day of chemotherapy and the start of chest RT for patients treated with concurrent chemoradiotherapy was 18.0 ± 11.1 days (range, −13 to 49). The overall treatment time of RT was 21 ± 3.7 days (range, 17–41). The median interval between the start of chemotherapy and the end of RT (SER) was 39 ± 34.0 days (range, 20–176). The median SER for patients treated with concurrent chemoradiotherapy was 38 ± 11.6 days (range, 7–71). Of the 60 patients, 50 (83%; 95% CI, 72–91%) received prophylactic cranial irradiation.

A difference in mediastinal staging according to CT and PET was observed in 30% (95% CI, 20–43%) of the 60 patients (Fig. 1). In 15% (95% CI, 8–26%), more nodal stations were involved on PET than on CT, and in 13% of patients (95% CI, 7–24%) fewer nodal stations were involved on PET than on CT. In 1 patient, nodal stations were involved on PET that were not involved on CT and *vice versa*. In 3 patients (5%; 95% CI, 2–14%), supraclavicular nodal stations were involved on PET, but the CT scan was negative for these stations.

Patterns of failure

An overview of the frequency and site of relapses is listed in Table 3.

The minimal follow-up of all surviving patients was 18 months. The median follow-up for all patients was 18.5 ± 10.3 months (range, 3-52). Of the 60 patients, 39 (65%, 95% CI, 52–76%) developed a recurrence.

Two patients (3%; 95% CI, 1–11%) experienced an isolated nodal recurrence. Both recurrences were treated with concurrent chemoradiotherapy. The first patient, whose primary tumor was located in the left lower lobe, developed a nodal recurrence in station 4R at 15 months after treatment. Different nodal stations had been involved before treatment on PET (stations 5 and 10L) and CT (station 10L), but station 4R was not involved before treatment on PET or CT. The second patient, with the primary tumor located in the lingula of the left lung, developed nodal recurrence in station 2L and the left supraclavicular region, also 15 months after treatment. Those stations were not involved before treatment on the basis of PET or CT (only station 6 involved).

In 87% (95% CI, 73–94%), distant metastases (either isolated or combined with local or nodal recurrence) were present at recurrence. Nine patients (15%, 95% CI, 8–26%) were diagnosed with isolated brain metastases, of whom 6 had previously received prophylactic cranial irradiation. A nodal recurrence outside the treatment field combined with recurrence inside the treatment field occurred in 5 patients (8%; 95% CI, 4–18%). In 1 of them, the nodal recurrence

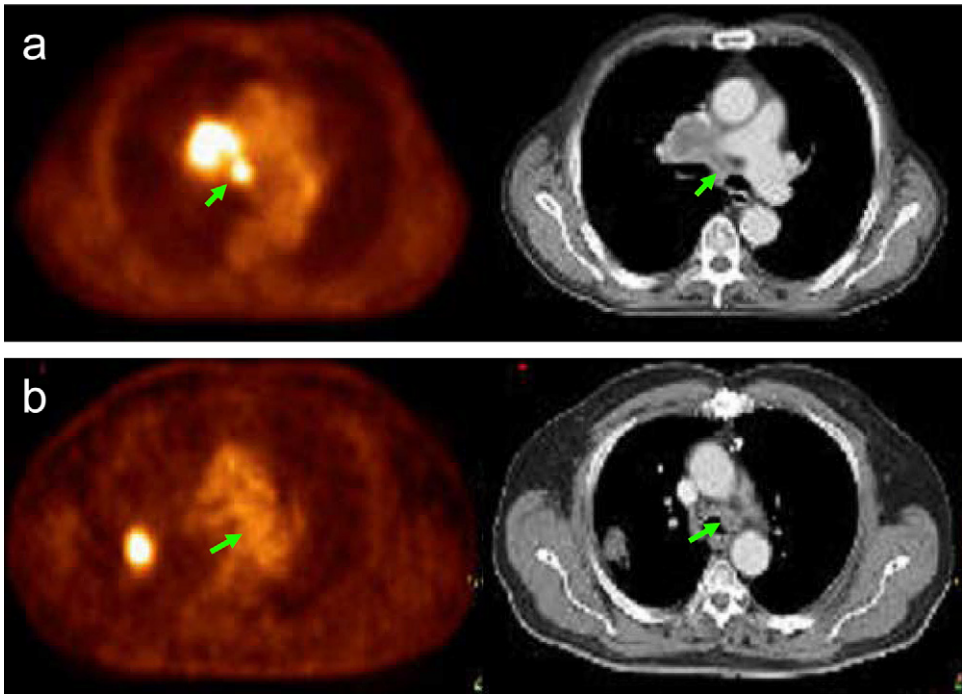

Fig. 1. Difference in involved nodal stations between positron emission tomography (PET) and computed tomography (CT). (a) Representative image of patient with positive nodal station 7 on PET, with negative findings on CT. (b) Representative image of patient with positive nodal station 4L on CT, with negative findings on PET.

occurred in a nodal station that was positive on CT, but negative on PET, and hence had not been included in the treatment field.

Survival

The median actuarial OS time for all patients was 19 months (95% CI, 17–21; Fig. 2), with a 2-year OS rate of 35% (95% CI, 24–48%). The median OS for patients treated with concurrent chemoradiotherapy was also19 months (95% CI, 16–22 months). The median actuarial PFS was 14 months (95% CI, 12–16; Fig. 3), with a 2-year PFS rate of 17% (95% CI, 9–28%).

Table 3. Frequency and location of recurrences as assessed by CT

Recurrence	Patients (n)
None	**21 (35)**
Local	**9 (15)**
In field	3 (5.0)
Out of field	4 (6.7)
Both in field and out of field	2 (3.3)
Isolated local	2 (3.3)
Local and distant/nodal	7 (11.7)
Nodal	**20 (33.3)**
In field	8 (13.3)
Out of field	7 (11.7)
Both in field and out of field	5 (8.0)
Isolated nodal	2 (3.3)
Nodal and distant/local	18 (30.0)
Distant	**34 (56.7)**
Isolated distant	19 (31.7)
Distant and local/nodal	15 (25.0)
Isolated brain	9 (15.0)

Abbreviation: CT = computed tomography.
Data in parentheses are percentages.

Toxicity

An overview of the dose volume histogram (DVH) parameters according to the toxicity grade is presented in Table 4. The mean DVH parameters were as follows: mean MLD: 12.9 ± 4.2 Gy; mean MED: 22.1 ± 8.6 Gy; mean Dmax: 44.5 ± 8.6 Gy. Treatment-related toxicity to the lungs was relatively mild, with Grade 3 cough in 1 patient and Grade 3 dyspnea in 2 patients. However, 62% of patients experienced acute esophagitis of Grade 2 or more, with 12% (95% CI, 6–22%) experiencing Grade 3 esophagitis. The frequency of Grade 3 esophagitis in patients treated with

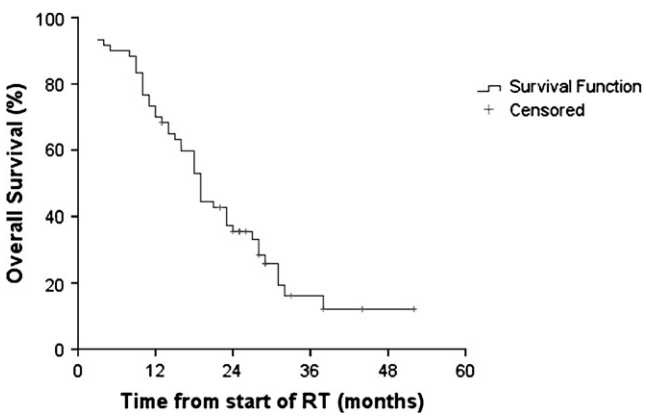

Fig. 2. Actuarial overall survival.

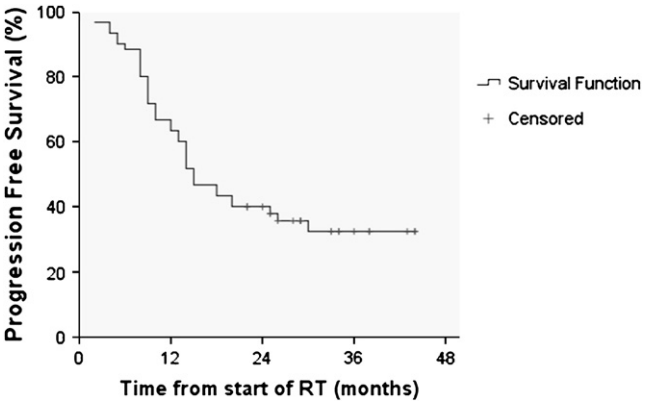

Fig. 3. Actuarial progression-free survival.

concurrent chemoradiotherapy was 13% (95% CI, 7–25%). No Grade 4 or 5 toxicity was observed. The esophagitis resolved within 4 weeks after RT in all patients. No significant correlation was found between the toxicity grade and the radiation parameters, neither for lung nor esophageal toxicity.

Table 4. Dose–volume histogram parameters according to toxicity grade*

Toxicity	Patients (*n*)	Parameter	
Lung toxicity			
Cough		MLD ± SD (Gy)	
G0	11 (18.3)	12.0 ± 4.1	
G1	34 (56.7)	13.8 ± 4.)	
G2	14 (23.3)	13.5 ± 3.3	
G3	1 (1.7)	6.9 ± 0.0	
Dyspnea		MLD ± SD (Gy)	
G0	22 (36.7)	11.8 ± 3.7	
G1	27 (45.0)	13.5 ± 3.9	
G2	9 (15.0)	15.2 ± 4.1	
G3	2 (3.3)	16.5 ± 3.4	
Esophageal toxicity			
Esophagitis		MED ± SD (Gy)	Dmax ± SD (Gy)
G0	9 (15.0)	14.6 ± 9.7	41.0 ± 10.2
G1	14 (23.3)	23.4 ± 9.3	44.1 ± 9.7
G2	30 (50.0)	22.9 ± 7.8	44.9 ± 3.4
G3	7 (11.7)	24.0 ± 6.8	47.0 ± 0.9

Abbreviations: MLD = mean lung dose; SD = standard deviation; G = grade; MED = mean esophageal dose; Dmax = maximal esophageal dose.

* Common Terminology Criteria for Adverse Events, version 3.0.

DISCUSSION

This is the first prospective study evaluating SNI based on FDG-PET scans in LD-SCLC patients.

In the absence of clinical evidence regarding the safety of SNI, radiation oncologists are confronted with the choice between a possible reduction in treatment-related toxicity and the possibility of increasing the risk of locoregional failure (11). A Phase II trial by our group evaluating the safety of CT-based SNI resulted in an unacceptably high percentage of isolated regional failures (11%; 95% CI, 2–29%). In contrast, in the present study, with SNI based on PET, isolated nodal recurrences occurred in 3% of patients (95% CI, 1–11%). This proportion is comparable to that found with SNI in NSCLC, in which about 2% experienced an isolated nodal recurrence with SNI on basis of FDG-PET scans (5, 6).

The remarkable difference between the value of SNI based on CT vs. PET in LD-SCLC may be explained by the discrepancy in the involved nodal stations on the PET and CT scans. Indeed, we observed different lymph node stations involved on PET compared with those on CT in 30% of our LD-SCLC patients. The proportion of patients in whom more nodal stations were involved on PET than on CT was similar to the percentage in whom fewer nodal stations were involved on PET than on CT. These data correspond to those found in the planning study we performed, in which a difference in involved nodal stations in 24% of patients was observed. In our prospective study concerning CT-based SNI for SCLC, all isolated nodal failures occurred in the ipsilateral supraclavicular area (12). The present study showed involvement of the ipsilateral supraclavicular nodes on PET in 5% of patients whose CT scan was negative for this region. This confirms that PET scanning can result in the up-front detection of supraclavicular lymph node metastases, thereby reducing the risk of an isolated nodal recurrence in this area.

Patients with an isolated nodal failure could theoretically have been cured if elective nodal irradiation had been performed instead of SNI. However, aside from the nodal recurrences, both local and distant recurrences still occurred in most patients, emphasizing the need for better treatment strategies for this disease.

The median OS in our study of 19 months (2-year OS rate, 35%) was lower than that reported in the trial by Turrisi *et al.* (1), in which LD-SCLC patients were treated with concurrent chemoradiotherapy with elective nodal irradiation (median OS of 23 months and 2-year OS rate of 47%). A possible explanation for this difference in survival is the relatively long SER in our study (39 days; range, 20–176). Moreover, the standard chemotherapy regimen in our region consisted of carboplatin-etoposide, not cisplatin-etoposide chemotherapy as in the trial by Turrisi *et al.* (1). Although one randomized prospective trial showed equal efficacy for both treatment regimens in the treatment of SCLC (31), no definitive conclusions could be drawn regarding the outcomes with concurrent chemoradiotherapy for LD-SCLC. Finally, in the trial by Turrisi *et al.* (1), patients with contralateral hilar or supraclavicular involvement were excluded, whereas they were included in our study.

Lung toxicity was generally mild and rare, with only 5% of patients experiencing Grade 3 toxicity (cough or dyspnea according to the Common Terminology Criteria for Adverse Events, version 3.0). A remarkably low percentage of severe acute esophagitis was found, with only 12% (95% CI, 6–22%) of patients experiencing Grade 3 esophagitis. In patients who have undergone elective nodal irradiation, or CT-based SNI,

Grade 3 esophagitis usually occurs in about 30% of patients (1, 6). This cannot be straightforwardly explained by a reduction in radiation fields, because both our previous planning study and the present trial showed an equal percentage of increases and decreases in radiation fields when using PET instead of CT. Possible hypotheses include the relatively long SER in the present study (32), a lower than average neutropenia level (33), which was not investigated in the present study, or simply an observation due to chance. If the current finding of lower esophageal toxicity holds true, PET-based SNI could provide opportunities for dose escalation and, hence, improvement of locoregional tumor control. Therefore, more studies are warranted to investigate this finding.

The use of FDG-PET-CT is likely to be the most accurate noninvasive staging method for the mediastinum in SCLC (15, 29, 34). However, the most reliable method to detect mediastinal nodal involvement remains pathologic verification. The available studies have indicated that CT underestimates mediastinal nodal involvement (35–37). No prospective data exist concerning correlation of the pathologic findings with PET findings in SCLC. Because of the low rate of isolated nodal failures found in the present study and the morbidity associated with invasive staging, we believe that our data support the use of PET-based SNI for LD-SCLC.

CONCLUSION

This prospective study shows that PET-based SNI in LD-SCLC is safe and is associated with low toxicity.

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